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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/12/2002 #25

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/533,906	COLLINS ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

~~Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.~~

- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 March 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,7,11,14,17*
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Reissue Applications

1. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 5,750,338 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

2. The patent sought to be reissued by this application is involved in litigation. It is noted that the following Notices Regarding Related Litigation have been entered and considered by the examiner: paper no. 3, filed March 10, 2000; paper no. 5, filed August 7, 2000; paper no. 16, filed January 31, 2001; paper no. 19 ½, filed July 16, 2001, and paper no. 21, filed August 24, 2001.

Any additional documents and/or materials which would be material to the patentability of this reissue application are required to be made of record in reply to this action.

Due to the related litigation status of this application, EXTENSIONS OF TIME UNDER THE PROVISIONS OF 37 CFR 1.136(a) WILL NOT BE PERMITTED DURING THE PROSECUTION OF THIS APPLICATION.

3. While there is concurrent litigation related to this reissue application, action in this reissue application will NOT be stayed because of applicant's request that the application be examined at this time. Due to the related litigation status of this reissue application, EXTENSIONS OF TIME UNDER THE PROVISIONS OF 37 CFR 1.136(a) WILL NOT BE PERMITTED.

Amendments

4. The following amendments have been entered into the instant application:

a) the Preliminary Amendment filed March 8, 2000, amending claim 19 and adding new claims 41-59;

b) the "Second Preliminary Amendment" filed August 23, 2001, amending col 1, lines 4-18 of the specification; and

c) the "Second Preliminary Amendment" filed October 24, 2001, amending col 1, lines 4-18 of the specification.

Consent of Assignee and Offer to Surrender

5. The Consent of Assignee, Offer to Surrender Original Patent, and Statement Under 37 CFR 3.73(b) and the Assignment from Amoco Corporation to Vysis filed March 8, 2000 have been entered.

6. This application is objected to under 37 CFR 1.172(a) as the assignee has not established its ownership interest in the patent for which reissue is being requested. An assignee must establish its ownership interest in order to support the consent to a reissue application required by 37 CFR 1.172(a). The assignee's ownership interest is established by:

(a) filing in the reissue application evidence of a chain of title from the original owner to the assignee, or

(b) specifying in the record of the reissue application where such evidence is recorded in the Office (e.g., reel and frame number, etc.).

The submission with respect to (a) and (b) to establish ownership must be signed by a party authorized to act on behalf of the assignee. See MPEP § 1410.01.

An appropriate paper satisfying the requirements of 37 CFR 3.73 must be submitted in reply to this Office action.

It is noted that Office records indicate that the instant application is currently assigned to Amoco Corporation. While a copy of an assignment from Amoco to Vysis executed in 1996 has been provided, this assignment has not been recorded and the Statement under 37 CFR 3.73(b) does not indicate that this document has been recorded or submitted for recording.

7. The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

Oath

8. The reissue oath/declaration filed with this application is defective (see 37 CFR 1.175 and MPEP § 1414) because of the following:

a) It does not identify the citizenship of each inventor.

b) It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

c) The reissue oath/declaration filed with this application is defective because it fails to identify at least one specific error which is relied upon to support the reissue application. See 37 CFR 1.175(a)(1) and MPEP § 1414.

It is noted that the declaration indicates that the error which is the statutory basis for reissue "is that the patent fails to contain claims of intermediate scope." However, MPEP 1414 II states that "Any error in the claims must be identified by reference to the specific claim(s) and the specific claim language wherein lies the error." Thus, Applicants are required to identify at least one error which is relied upon in this specific manner.

It is further noted that Applicants' statement with respect to whether the patentee claimed more or less than patentee had the right to claim should be consistent with the nature of the specific error(s) identified in the declaration.

d) The reissue oath/declaration filed with this application is defective because it fails to contain a statement that all errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant. See 37 CFR 1.175

and MPEP § 1414. The statement in Applicants' declaration is incomplete and fails to comply with all the requirements of 37 CFR 1.175.

9. In accordance with 37 CFR 1.175(b)(1), a supplemental reissue oath/declaration under 37 CFR 1.175(b)(1) must be received before this reissue application can be allowed.

Claims 1-59 are rejected as being based upon a defective reissue declaration under 35 U.S.C. 251. See 37 CFR 1.175. The nature of the defects are set forth above.

Receipt of an appropriate supplemental oath/declaration under 37 CFR 1.175(b)(1) will overcome this rejection under 35 U.S.C. 251. An example of acceptable language to be used in the supplemental oath/declaration is as follows:

> "Every error in the patent which was corrected in the present reissue application, and is not covered by a prior oath/declaration submitted in this application, arose without any deceptive intention on the part of the applicant."

Claim Objections

10. Claims 35-37 are objected to because of the following informality in claim 35: the claims recites the phrase "wherein the target polynucleotide is amplified a polymerase" rather than, e.g., "wherein the target polynucleotide is amplified with a polymerase". Appropriate correction is required.

Specification

11. The disclosure is objected to because of the following informalities. As a result of the Certificate of Correction granted in original Patent 5,750,338 on December 25, 2001, Applicants' amendments to the "Continuing" information at col 1, lines 4-18 are improper. It is noted that Certificate of Correction changes granted in the original patent should be entered in the reissue application without bracketing or underlining; only changes to be made in the reissue as compared to the original patent should be bracketed/underlined. It is further noted that in the instant case, the Certificate of Correction granted in the '338 patent on December 25, 2001 is improper, because: a) that patent is not a reissue application, and b) no reference to reissue should be included in the "Continuing" information, as the face of a granted reissue indicates the fact that the patent is a reissue. Accordingly, Applicant is advised to amend the instant specification so as to recite the Continuing information set forth in Patent 5,750,338 as of 12/25/01 but providing for the deletion of the phrase "is a Reissue of Ser. No. 238,080, filed May 3, 1994, now U.S. Patent No. 5,750,338, which" by presenting that phrase in brackets.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-59 are indefinite over the recitation of the term "amplifying" and over the recitation of the phrases "wherein the target polynucleotide is amplified *in vitro* to produce a multitude of polynucleotide amplification products" in claims 41, 47, 53, and 56-59 and "wherein the means for amplifying provide for *in vitro* amplification of the target polynucleotide to produce a multitude of polynucleotide amplification products" in claims 54-55. As discussed below in the section of this Office action entitled "Protest," the teachings of the specification and of the prior art, as well as Applicants' admissions on the record, indicate that the types of "amplifying" that are intended to be encompassed by the instant claims are limited to *in vitro* types of amplification. However, Applicants have proposed adding dependent claims that recite the further requirements for "amplifying *in vitro*" and "*in vitro* amplification" set forth above. While the teaching of the specification and of the art and Applicants' admissions suggest one meaning of "amplifying," Applicants' proposed amendments suggest the possibility that the term "amplifying" when used alone may have a different meaning. Accordingly, one of skill in the art cannot determine the metes and bounds of the claimed invention, and it is unclear as to how claims 41-59 are intended to be further limiting of the claims from which they depend. This rejection could be overcome by amending all the claims so as to clearly limit them to *in vitro* amplification

(e.g., by amending "amplifying" to "amplifying *in vitro*" in claims 1, 7, 19, 20, 24, 27, 28, 34, and 38, etc.).

Claims 1-19 and 41-53 are indefinite over the recitation of the term "the target polynucleotide" in step c of claims 1, 7, and 19. The steps of claims 1, 7, and 19 preceding step c refer to both a "target polynucleotide" and a "bound target polynucleotide" (which is recited in the step immediately preceding step c). It is unclear as to whether applicants' intent is to refer back to "the target polynucleotide" of (a), the "bound target polynucleotide" of (b), etc. Clarification is required.

Claims 4-6, 10-12, 17-18, 29-33, 35-37, 39-53, and 56-59 are indefinite over the recitation of the phrase "The method .... wherein the target polynucleotide is amplified..." in claims 4, 10, 17, 29, 32, 35, 39, 41, 46, 47, 53, and 56-59, "The amplification method...wherein the target polynucleotide is amplified...." in claims 44 and 46, and "The detection method....wherein the target polynucleotide is amplified" in claims 50 and 52. It is unclear as to whether applicants' intent is to further limit an "amplifying" step (or steps) recited in a preceding claim, whether applicants' intent is to require additional steps of amplification of "target polynucleotide" at some other point in the claimed method (or at any time), etc. Clarification is required.

Claims 7-19, 38-40, 47-53, and 59 are indefinite for failing to recite a final process step that clearly relates back to the claim preamble. The claims are drawn to methods "for detecting a target polynucleotide" yet recite a final process step of detecting an "amplified target polynucleotide". The claims do not set forth

how detection of an amplified target polynucleotide relates back to detection of "the target polynucleotide". This rejection could be overcome by amending the claims to recite, e.g., "detecting the presence of the amplified target polynucleotide as indicative of the presence of the target polynucleotide in said sample".

Claims 13-16 are indefinite because it is unclear as to how the limitations recited in claims 13-16 are intended to further limit the claims, particularly how the limitations are intended to relate to the objective of detecting a target polynucleotide. For example, how do steps of contacting "the amplified target polynucleotide" with a label, a labeled probe, or a second support relate to detection of amplified target polynucleotide and detection of the target polynucleotide?

Claims 19 and 53 are indefinite because it is unclear as to how steps d and e of claim 19 relate to one another. Particularly, it is unclear as to how the step of "detecting the presence of the amplified target polynucleotide" (step e) relates to or results from the "contacting" of step d. Clarification is required.

Claims 20-23 and 54 are indefinite over the recitation of the limitation "the amplified target polynucleotide" in claim 20. There is insufficient antecedent basis for this limitation in the claims.

Claims 21-23 are indefinite over the recitation of the limitation "the means for binding that amplified target polynucleotide to a solid support' in claim 21. There is insufficient antecedent basis for this limitation in the claims.

Claims 21-23 are indefinite because it is unclear as to whether the recitation "a detector probe for labeling...." is intended to be a further requirement of "the means for binding" of c, whether applicants' intend for the claim to further inclusion of a detector probe in the kit, etc.

Claims 22-23 are indefinite over the recitation of the limitation 'the target" in claim 22. There is insufficient antecedent basis for this limitation, and it is unclear as to whether applicants intend to refer back to "the target polynucleotide", "the amplified target polynucleotide", etc.

Claims 27-33 and 56-57 are indefinite over the recitation of the terms "the target" in step a of claims 27 and 28 and "the target polynucleotide" in step g of claims 27 and 28. First, there is insufficient antecedent basis for the recitation "the target". Second, it is unclear as to whether the recitation of "the target polynucleotide" in step g is intended to refer to "the target polynucleotide" recited in the claim preamble, "the target" recited in step a, or to, e.g., target polynucleotide that might be present in the medium of step f. Clarification is required.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 20-26 and 54-55 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Erlich et al (U.S. Patent No. 5,468,613 [11/21/1995; effective filing date 8/22/1986]).

Erlich et al teach kits comprising primers, polymerization agents, nucleoside triphosphates, labeled oligonucleotide probes, supports, and probes attached to supports (see entire reference, particularly col 3, line 61-col 4, line 18; col 18, lines 13-28; and claims 24-32). The primers, polymerization agents, and nucleoside triphosphates taught by Erlich et al constitute a "means for amplifying" a target polynucleotide, as required by the instant claims. The probe attached to a support disclosed by Erlich et al constitutes both a "means for substantially separating" a target polynucleotide from a sample and a "means for binding" amplified target polynucleotide to a solid support (see in particular col 17, lines 6-43, and claims 29-32). The labeled probes disclosed by Erlich et al constitute a "means for labeling" amplified target polynucleotide, as do the labeled primers and/or nucleoside triphosphates taught by the reference (see, e.g., col 3, lines 51-53). With respect to claims 21-23 and 26, it is noted that the probe affixed to a membrane disclosed by Erlich et al constitutes a "capture probe which binds to" a "solid support" and to "amplified target polynucleotide"/ "target polynucleotide", as required by the claims. With respect to claims 21-23 and 25-26, it is noted that the polymerization agents disclosed by Erlich et al include DNA polymerases (see, e.g., col 8, lines 50-60 and claims 26 and 31). With respect to claims 54-55, the "means for amplifying" disclosed by Erlich et al (specifically, the primers, polymerization agents, and nucleoside triphosphates

discussed above) "provide for *in vitro* amplification....to produce a multitude of polynucleotide amplification products," as required by the claims. Accordingly, Erlich et al clearly anticipate the instant claims.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 20-26 and 54-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlich et al (U.S. Patent No. 5,468,613 [11/21/1995; effective filing date 8/22/1986]) in view of Snitman et al (U.S. Patent No. 5,273,882 [12/28/1993; effective filing date June 13, 1985]).

This rejection applies to the claims to the extent that they may be limited to kits comprising "retrievable" supports; i.e., supports of the type described in the instant specification at col 1, lines 60-64, which "can be substantially dispersed within a medium and removed or separated from the medium by immobilization, filtering, partitioning, or the like."

Erlich et al teach kits comprising primers, polymerization agents, nucleoside triphosphates, labeled oligonucleotide probes, supports, and probes attached to supports (see entire reference, particularly col 3, line 61-col 4, line 18; col 18, lines 13-28; and claims 24-32). The primers, polymerization agents, and nucleoside triphosphates taught by Erlich et al constitute a "means for amplifying" a target polynucleotide, as required by the instant claims. The labeled probes disclosed by Erlich et al constitute a "means for labeling" amplified target polynucleotide, as do the labeled primers and/or nucleoside triphosphates taught by the reference (see, e.g., col 3, lines 51-53). The probe attached to a support disclosed by Erlich et al constitutes both a "means for substantially separating" a target polynucleotide from a sample and a "means for binding" amplified target polynucleotide to a solid support (see in particular col 17, lines 6-43, and claims 29-32). With respect to claims 21-23 and 26, it is noted that the probe affixed to a membrane disclosed by Erlich et al constitutes a "capture probe which binds to" a "solid support" and to "amplified target polynucleotide"/ "target polynucleotide", as required by the claims. With respect to claims 21-23 and 25-26, it is noted that the polymerization agents disclosed by Erlich et al include DNA polymerases (see, e.g., col 8, lines 50-60 and claims 26

and 31). With respect to claims 54-55, the "means for amplifying" disclosed by Erlich et al (specifically, the primers, polymerization agents, and nucleoside triphosphates discussed above) "provide for *in vitro* amplification....to produce a multitude of polynucleotide amplification products," as required by the claims. Erlich et al do not teach retrievable solid supports or capture probes that bind to such supports and to amplification products. Snitman et al disclose kits comprising dispersible solid supports associated with capture probes (see entire reference, particularly col 5, lines 8-22 and 35-47; col 7, lines 18-25; col 15, lines 1-4). Snitman et al disclose that such supports and capture probes may be used to capture hybridization complexes in solution (see, e.g., col 4, line 50-col 5, line 7, and col 5, lines 23-34). Snitman et al disclose that the use of dispersible supports and capture probes to detect hybridization in solution provides an advantage over hybridization to a membrane, as taught by Erlich et al, because hybridization in solution "proceeds more quickly" and because "complex formation is much more rapid than hybridization". Accordingly, in view of the teachings of Snitman et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the kits of Erlich et al so as to have included therein the dispersible supports and associated capture probes taught by Snitman et al, or so as to have substituted the supports and probes of Snitman et al for the probe affixed to a membrane disclosed by Erlich et al. An ordinary artisan would have been motivated to have made such a modification in order to have provided practitioners with reagents

that would allow for more rapid detection of hybridization, for the advantages of increased efficiency and convenience.

Allowable Subject Matter

18. The prior art does not teach or suggest methods for amplifying or detecting a target polynucleotide in which a sample is contacted with a solid support that binds the target polynucleotide, the support and bound polynucleotide are "substantially" separated from the sample, and the "retrieved" polynucleotide is amplified. The instant specification teaches that:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, **can** employ non-specific enzymes **or** primers (i.e., enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence). Although any background, non-target nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus **no specially tailored primers are needed** for each test, and the same standard amplification reagents can be used, regardless of the targets.
> (col 30, lines 30-40; **emphasis added**)

Thus, the specification discloses that the methods of the claims provide an advantage over prior art methods of detection/amplification in that targets captured by applicants' methods, which targets are of known identify due to the use of specific capture probes, may be amplified non-specifically, thereby allowing one to employ a standard set of reagents during the amplification step. Applicants' disclosure at col 30, lines 30-40, also makes clear, via the recitations "**can** employ non-specific enzymes **or** primers" and "no specially tailored primers are **needed**," that methods of specific amplification may also be employed following capture. Thus, Applicants' methods are also advantageous in that the

capture step employed allows one to readily amplify target molecules in either a specific or non-specific manner, depending on, e.g., what reagents are most readily available to a practitioner. As the identity of the polynucleotide to be amplified is determined by the capture step, the manner in which the amplification is accomplished is not critical. Further, Applicants disclose that their method provides an advantage in allowing one to avoid amplification of "background" or non-target molecules by first separating a particular target molecule of interest from a sample. As the identity of the molecule being amplified is known, applicants methods further allow one of skill in the art to avoid such steps as, e.g., confirmatory hybridization following amplification.

With respect to methods of detection comprising steps of both amplification and hybridization with an immobilized probe, the closest prior art reference, Syvanen et al (Nucleic Acids Research 14(12):5037-5048 [6/1986]), discloses methods in which target nucleic acid sequences of interest are retrieved from crude biological samples using capture probes that are collected on a streptavidin-agarose matrix, then detected and quantitated (see entire reference, especially p. 5045). Syvanen et al suggest that the sensitivity of their assay may be increased by amplification of target DNA prior to detection by their method (see p. 5044). The "amplifying" reference referred to be Syvanen et al is Saiki et al (Science 230(4732):1350-1354 [12/1985]), which discloses PCR, a method for amplifying a particular target polynucleotide in which specific primers are employed in enzymatic amplification of the target by repeated cycles of annealing, extension, and denaturation (see entire reference). However, while

Syvanen et al suggest that an initial step of amplification may be used to enhance the detection sensitivity of their methods, Syvanen et al do not teach or suggest a method in which, e.g., the hybrids that result from their detection/quantitation method are further processed by, e.g., separation and amplification of target sequences. In fact, the successful performance of Syvanen et als' methods requires a final step of hybrid detection in order to achieve quantitative detection. Similarly, Snitsky et al (U.S. Patent No. 5,008,182 [4/1991; effective filing date 11/1986]) disclose detection of amplification products by capture of those products using an immobilized probe (see, e.g., col 15, lines 43-47). Thus, the closest prior art references would have led one of skill in the art to have performed amplification followed by detection by capture/hybridization, rather than capture of a specific target followed by amplification, as in Applicants' invention.

Further, with respect to methods of nucleic acid amplification, it is noted that in the method of Saiki et al, specificity is achieved by employing particular primers in the amplification, and the reference discloses that "DNA samples of poor quality....can give excellent results" (p. 230, top of left column). Accordingly, there is no suggestion in Saiki et al to add a step of target capture prior to amplification, in order to, e.g., improve amplification in some way by improving the purity or quality of the target to be amplified. Additionally, it is noted that Saiki et al (Nature 324(6093):163-166 [11/1986]) disclose that PCR may be performed on crude cell lysates (see entire reference). While Saiki et al do suggest that debris in samples containing large number of cells may inhibit

amplification, the reference demonstrates that the mere dilution of such a sample is sufficient to permit amplification (p. 164-165; Figure 3). Accordingly, with respect to amplification of a particular target polynucleotide of interest, the teachings of the prior art would have led one of skill in the art to have employed the specific amplification methods of the Saiki et al references directly on a sample (diluted if necessary) containing the target; the art would not have motivated one to have added the additional capture step required by the instant claims. It is also noted that the prior art discloses a variety of methods of non-specific *in vitro* enzymatic amplification of a polynucleotide target, which methods may be practiced on nucleic acids purified by a variety of methods. However, the prior art does not teach or suggest the particular advantages of target capture prior to amplification disclosed by applicants, specifically, that by first capturing a particular target polynucleotide, one may then amplify that polynucleotide in either a specific or non-specific manner, and further avoid amplification of background non-target molecules, as discussed above.

Protest

19. It is noted that the Protest under 37 CFR 1.291(a) filed August 2, 2000, paper no. 7 ("the Protest"), has been considered. Further, all documents cited on the PTO Form 1449 included as part of paper no. 7 have been considered; an initialed and signed copy of that Form 1449 is included with this Office action.

20. It is noted that the response to the above Protest filed by Applicants' January 16, 2001, paper no. 11, and the corrected version thereof filed January

23, 2001, paper no. 13 ("the Response"), have been considered. Further, all documents cited on the PTO Form 1449 included as part of paper no. 11 have been considered; an initialed and signed copy of that Form 1449 is included with this Office action. The documents considered include the Declaration of David J. Lane, Ph.D. (reference number 27 in the IDS of paper no. 11).

21. Each of the major points raised in the Protest and discussed in the Response are discussed below in the order set forth in the Protest.

22. First, it is noted that Applicants have acknowledged that they consider December 12, 1987 to be the priority date to which they are entitled with respect to the pending claims (see Interview Summary, paper no. 12).

23. With respect to the points raised in Section IA of the Protest, it is acknowledged that methods in which probes immobilized on dispersible supports are used to separate/isolate and/or detect polynucleotides were known in the art prior to December 21, 1987.

24. With respect to the points raised in Section IB of the Protest, it is acknowledged that a variety of methods of *in vitro* amplification were known in the art prior to December 21, 1987.

The Protest asserts that the definition of the term "amplify" in applicants' specification "includes any process by which copies of target polynucleotide are produced or by which other molecules....are produced by virtue of the presence of the target polynucleotide," referring to col 2, lines 9-19. The Protest also asserts that "applicants' broad definition encompasses processes such as cloning, cell-free translation and synthesis of cDNA from mRNA."

The argument in the Protest with respect to the breadth of the term "amplify" as used by applicants is not persuasive. Claims are given the "broadest reasonable interpretation" that is consistent with the teachings and guidance provided by the specification and that is consistent with "the interpretation that those skilled in the art would reach" (see MPEP 2111). The definition at col 2, line 9, states "The term 'amplify' is used in the broad sense to mean creating an amplification product which may include **by way of example**....." (**emphasis added**). The definition goes on to provide examples of amplification products; such examples are non-limiting, thus, the broadest aspect of applicants' definition is the statement "creating an amplification product". It is noted that the types of amplification exemplified by applicants are limited to *in vitro* enzymatic amplification; thus, the types of "amplifying" and amplification products exemplified by applicant are methods of *in vitro* enzymatic amplification and products thereof, respectively. Further, Applicants refer in the specification to products of non-specific *in vitro* enzymatic amplification as "amplification products"; see, e.g., col 15, lines 56-58: "In Step 3 of FIGS. 4, 5, and 6, the isolated target is non-specifically amplified to form a multitude of amplification products"). As a limiting definition of the term "amplification product" is not provided in the specification, the broadest reasonable interpretation of this language can be established by considering the meaning of this term to those skilled in the art at the time the invention was made. The examples and statements in the specification noted above make clear that this term may be used to refer to products of non-specific *in vitro* enzymatic amplification. Further,

a search of the art at the time the invention was made indicates that this term was also well known to those of skill in the art as a term describing products of specific *in vitro* enzymatic amplification. For example, a search of the USPTO database indicates that at the time the invention was made the term "amplification product" referred to products synthesized via specific *in vitro* enzymatic amplification (see Erlich et al, U.S. Patent No. 6,194,561 (2/2001; filed 11/1987), col 24, line 55; Gelfand et al, U.S. Patent No. 4,889,818 (12/1989; filed 6/1987), col. 35, line 2; and Mullis et al, U.S. Patent No. 4,965,188 (10/1990; filed 6/1987), col. 5, lines 10 and 12, and col. 23, lines 48 and 61). Similarly, a search of Medline databases for references published in 1987 and 1988 employing the term "amplification product" also indicates that this language referred to a product of specific *in vitro* enzymatic amplification (see the abstracts of Amselem et al (Am. J. Hum. Gen. 43;95-100 [7/1988; submitted 1987 and accepted 1988]), Harbath et al (DNA 7(4):297-306 [5/1988; submitted and accepted 1987]), Shibata et al (J. Inf. Dis. 158(6):1185-1192 [12/1988; submitted 1987, submitted and accepted 1988]), Newton et al (Nucleic Acids Res. 16(17):8233-8243 [9/1988; submitted and accepted 1988), and Medlin et al, Gene 71;491-499 [11/1988, submitted and accepted 1988]). The search conducted by the examiner did not reveal references in which the term "amplification product" referred to any molecule that was not a product of *in vitro* enzymatic amplification, and thus did not provide any evidence that one of skill in the art might have interpreted the language "creating an amplification product" as encompassing methods other than *in vitro* methods of enzymatic amplification.

Further, it is noted that Applicants have acknowledged on the record that the term "amplifying" as used in their claims is intended to be limited to *in vitro* amplification (see page 4 of the Interview Summary of paper no. 12, and p. 14-17 of the Response of paper no. 13, in which Applicants state, e.g., 'While the text of the patent contains a general definition of amplification (col 2, lines 9-19), that definition does not indicate that the term includes *in vivo* methods," "the description of the actual steps of amplification in the remainder of the specification leaves no doubt that it is an *in vitro* enzymatic step," "there is no doubt that [the term "amplifying"] connotes an *in vitro* enzymatic process," etc.). Accordingly, in view of the guidance and teachings provided by the specification, as well as Applicants' own admissions with regard to the meaning of the term "amplifying," and considering the "interpretation that those skilled in the art would reach" with respect to the meaning of the term "amplifying" as used by applicants, it is clear that the term "amplifying" as used in the instant specification is limited to methods of *in vitro* enzymatic amplification.

25. In Section IC of the Protest, Protestor asserts that the prior art "explicitly suggests combining the isolation of a target polynucleotide from a sample by capture on a solid support with subsequent amplification of the isolated polynucleotide."

With respect to the Brown et al reference, the Protest argues that Brown et al's Concluding Remarks "teach the desirability of combining target isolation with a subsequent amplification step, particularly where the target polynucleotide is present in the initial sample at low concentration," referring to a passage on p.

687 of Brown et al. However, while Brown et al do disclose methods of purification employing solid supports and suggest increasing the quantity of a purified structural gene, the disclosure of Brown et al suggests that purification would preferably be followed by cloning. Particularly, the passage cited by Protestor concludes with the following statements: "Alternatively, insertion of the DNA into a phage or bacterial episome...could produce large amounts of homogeneous DNA components. This last method has the advantage of cloning individual DNA molecules from an impure mixture of DNA." While Brown et al do speculate that amplification "might be carried out in vitro by an efficient DNA polymerase," no guidance is provided with respect to how such a method might be carried out. The reference, which was published in 1974, does not adequately enable a method of amplifying *in vitro* the purified target DNA. Further, Brown et al clearly suggest that cloning has an advantage that *in vitro* amplification would lack. Thus, the Brown et al reference would have led one of skill in the art to have practiced a method of purification followed by cloning, rather than purification followed by an amplification that "might be carried out in vitro by an efficient DNA polymerase." It is also noted that Brown et al speculate about a method in which amplification "might be carried out in vitro by an efficient DNA polymerase" after purification has first "enriched the gene sequence about a thousandfold"; the reference does not disclose or suggest the advantages or features of applicants' invention, which allows a captured target molecule to be immediately amplified in either a specific or non-specific manner (see "Allowable Subject Matter").

With respect to the Arsenyan et al reference, it is noted that Arsenyan et al teach capture followed by cloning and growing transformants. For the reasons discussed above, the broadest reasonable interpretation of the term "amplifying" as used in applicants' claims and specification does not encompass amplification by cloning and growing transformants.

With respect to the Syvanen et al reference, it is noted that the teachings of this reference are discussed in the section of this Office action entitled "Allowable Subject Matter."

26. With respect to the points raised in Section II of the Protest, it is noted that the subject matter considered to be allowable in the instant application and the reasons for the allowability of that subject matter are discussed in the section of this Office action entitled "Allowable Subject Matter." It is also noted that the Brown et al and Arsenyan et al references are discussed above. With respect to the Persing declaration and the allowance of the '338 patent, it is acknowledged that Applicants' claims encompass "amplifying" by both specific and non-specific methods of *in vitro* enzymatic amplification, as discussed above. It is also acknowledged that the presence of polymerase inhibitors in biological samples was known at the time the instant invention was made. However, with respect to Saiki et al (Nature 324;163-6 [1986]), it is noted that the Saiki et al reference discloses that at the time the instant invention was made, practitioners believed that dilution of a sample was sufficient to overcome the effects of such inhibitors, as discussed in the section of this Office action entitled "Allowable Subject Matter."

27. With respect to the points raised in Section III of the Protest, it is again noted that Arsenyan et al teach capture followed by cloning and growing transformants. For the reasons discussed above, the broadest reasonable interpretation of the term "amplifying" as used in applicants' claims and specification does not encompass amplification by cloning and growing transformants. With respect to the Gaubatz et al reference, Gaubatz et al do not disclose capture of a nucleic acid followed by amplification of that nucleic acid, but rather capture of a nucleic acid followed by synthesis of a second nucleic acid having different structural properties than the captured molecule, which second nucleic acid is subsequently copied (see entire reference, particular Figure 1). Specifically, the molecule captured by Gaubatz et al is a globin mRNA (see, e.g., p. 176, right column) , while the copied molecule is a cDNA including a hairpin loop sequence flanked by inverted repeats of globin sequences, and a poly(dC) tail (see, e.g., p. 176-177, Figure 1). With respect to the Boss et al reference, Boss et al disclose sequencing a portion (the 5' end) of a captured molecule, but not amplification of that molecule within the meaning of "amplifying" as used in the instant specification. With respect to the Powell et al reference, it is noted that Powell et al do not teach a step of "substantially separating the support and bound target polynucleotide from the sample," which is required by claim 1. Rather, Powell et al disclose enrichment of a population of molecules (poly (A)+ RNA) by binding to oligo (dT) cellulose (p. 839). The composition resulting from such an enrichment includes large numbers of molecules from the sample subjected to enrichment, and such a step does not constitute substantial

separation of a particular "target polynucleotide" bound to a support from the original sample.

28. Section IV of the Protest asserts that Applicants' newly presented claims 41-59 lack support in the disclosure of the '338 patent.

It is first noted that the meaning of the term "amplify" as employed in applicants' claims and specification is discussed above. It is acknowledged that the specification only exemplifies target capture followed by non-specific methods of *in vitro* enzymatic amplification. However, by stating that "Amplification....**can** employ non-specific enzymes **or** primers" and "no specially tailored primers are **needed**," Applicants clearly also disclose methods in which "specifically tailored primers" are in fact used. In fact, Applicants disclose methods employing specific primers in teaching that their methods are advantageous because such primers are not required. The teachings of the specification would not have led a skilled artisan to conclude that applicants' methods could not or should not be practiced with specific primers, but rather that one could choose to avoid the use of such primers if doing so was, e.g., more convenient for the practitioner. Further, it is noted that because the term "amplification product" was primarily employed in the art at the time the invention was made as a term for describing PCR products (see discussion above), one of skill in the art would clearly have interpreted Applicants' use of this term in the phrase "creating an amplification product" as encompassing products of specific *in vitro* enzymatic amplification.

Declaration

29. The Protest of paper no. 7 includes the Declaration of Michael M. Harpold, Ph.D. ("the Harpold Declaration"), which Declaration has been considered by the examiner. The major points raised by and references discussed in the Harpold Declaration are discussed above in the section of this Office action entitled "Protest."

Response to Interview Summary

30. The Response to Interview Summary filed January 31, 2001, paper no. 15, has been considered by the examiner. It is noted that the specification discloses both specific and non-specific methods of *in vitro* enzymatic amplification, as discussed above. Further, applicants' specification disclose the fact that capture in combination with amplification provides for increased sensitivity of detection (see col 30, lines 15-17), the fact that "the presence of proteins and other molecules carried in biological samples may interfere" with enzyme activity (col 4, lines 12-14), and the fact that separation of a support to which a target molecule is bound facilitates separation of the target from cellular debris (see, e.g., col 5, lines 21-22; col 12, lines 8-15). A complete explanation of subject matter considered to be allowable and of reasons for allowability is provided in the section of this Office action entitled "Allowable Subject Matter." With respect to Applicants comments regarding the kit claims, it is noted that the examiner has interpreted the means-plus-function elements of the kit claims in light of the specification.

Information Disclosure Statements

31. It is noted that the examiner commented above on the Information Disclosure Statements filed with paper nos. 7 and 11.

32. The Information Disclosure Statement filed by applicants on March 8, 2000, paper no. 4, has been considered. An initialed and signed copy of the PTO Form 1449 of paper no. 4 is included with this Office action.

33. The Information Disclosure Statement filed by applicants on January 31, 2001, paper no. 14, has been considered. Initialed and signed copies of the 2 PTO Forms 1449 of paper no. 14 are included with this Office action.

34. The Information Disclosure Statement filed by Gen-Probe Incorporated on March 26, 2001, paper no. 17, has been considered. An initialed and signed copy of the PTO Form 1449 of paper no. 17 is included with this Office action.

Conclusion

35. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Impraim et al (Biochem. Biophys. Res. Comm. 142(3) :710-716 [2/1987]) disclose PCR amplification of nucleic acids obtained from fixed, paraffin-embedded tissues (see entire reference). Gebeyehu et al (U.S. Patent 4,921,805 [5/1990 ; effective filing date 6/1987]) disclose methods of isolating nucleic acids in which molecules are captured by an intercalator attached to a solid support (see entire reference, especially, e.g., col 3, lines 39-54). Urdea et al (EP225807A2 [6/16/87]) disclose kits comprising labeled probes

complementary to a target molecule sequence, "capturing" probes complementary to a target molecule sequence, and "support means," which support means are used to retrieve target molecules via a capturing probe complex (see entire reference, particularly page 28, claim 5). The support means disclosed by Urdea et al include, e.g., latex and glass particles (see p. 5, lines 26-30). It is also noted that the following references, which were cited during the prosecution of U.S. Patent No. 5,750,338 but not cited on any PTO Form 1449 entered into this application, have been considered by the examiner: Urdea et al (U.S. Patent No. 5,200,314 [4/1993]); Longiaru et al (U.S. Patent No. 5,232,829 [8/1993]) and Hansen (EP139489 [5/1985]).

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:00 am-3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/305-3014 for regular communications and 703/305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
February 1, 2002

CARLA J. MYERS
PRIMARY EXAMINER